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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,169	NEW, ROGER R. C.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 18-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 18-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-15 and 18-26 are pending; claims 16 and 17 were canceled by Applicant in the amendment file 10/27/2006.

Claim Objections

2. Claim 5 is objected to. The phrase "non-conjugated bile salt/additive" should be changed to "non-conjugated bile salt+additive" to be consistent with the phrase "b+c".

3. Claim 12 is objected to because chenodeoxycholate refers to the salt not acid form of the compound.

4. Claim 23 is objected to for the dash after "the" in the second line of the claim.

Claim Rejections - 35 USC § 112/101

5. The rejection of claims 18-23 is dropped in light of the amendment filed 10/27/2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-10, 12-15, 18-20, and 22-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

7. Claims 1-10, 12-15, 18-20, and 22-26 are drawn to pharmaceutical compositions comprising an active macromolecular principle, a bile salt and an additive. The specification discloses only compositions comprising insulin as the macromolecular principle. The specification does not provide examples of other specific proteins, polynucleotides or polysaccharides in compositions with a bile acid and additive, or guidance on how to make specific compositions with active ingredients other than insulin. The specification recites a laundry list of possible proteins and polynucleotides but it does not include evidence that representatives of this genus are actually used in the claimed composition. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

8. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

9. With the exception of the compositions including insulin, the skilled artisan cannot envision the detailed chemical structure of the macromolecular principle/bile acid/ additive composition. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. The compound

itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

10. Therefore, only the compositions including insulin, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

11. Claims 1-10, 12-15, 18-20, and 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for composition with insulin as the active macromolecular principle, does not reasonably provide enablement for compositions with all other protein, polynucleotides and polysaccharides as active macromolecular principles. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and are as follows:

The Nature of the Invention

12. The claims are drawn to pharmaceutical compositions comprising an active macromolecular principle, a bile salt and an additive. Methods for administering the compositions are also claimed.

The State of the Prior Art and its Predictability or Unpredictability

13. The use of bile salts to enhance the permeability of macromolecular drugs is well-known in the prior art (see for example New, U.S. Patent No. 5,853,748). The use of propyl gallate and

butyl hydroxyl anisole as antioxidants in pharmaceutical compositions is also well-known in the prior art (see Makino *et al.* JP 56138168A, abstract; Modi *et al.* U.S. Patent No. 5,653,987, column 3, lines 33-36; and Desai U.S. Patent No. 5,206,219, column 5, lines 5-18). The use of insulin as a pharmaceutical agent is likewise well-known in the prior art.

14. Less well-known and less predictable are the use of other protein and polynucleotide based drugs. Therapies involving DNA and RNA in particular are notoriously unpredictable. Liu *et al.* (*World J. Gastroenterol.*, **2006**, *12*, 6941) write: "Up till now, researches on anti-angiogenesis cancer gene therapy remain in pre-clinical stage. It is anticipated that when better vectors are developed and the molecular mechanisms of angiogenesis inhibitors against tumor growth are better understood, clinical trials will be undertaken in the future."

15. Sutter *et al.* (*World J. Gastroenterol.*, **2006**, *12*, 380) also comment on the unpredictability associated with gene therapy: "cancer gene therapy will increase its importance as a therapeutic tool even though many problems still need to be solved. One of the most important issues affecting the possible clinical application of gene therapy is the need to ensure the highest possible safety levels. Many clinical investigations have demonstrated that the currently available vector systems are well tolerated and side effects are acceptable. However, the use of retroviral vectors is discussed controversially, since 3 of 11 children with X-linked severe combined immunodeficiency, who were treated with a retrovirus, developed uncontrolled T-lymphocyte proliferation in a French gene therapy trial. The major problem of cancer gene therapy that still remains is the relatively poor therapeutic outcome. This problem is not restricted to a specific tumor entity, but is rather a general problem. There may be many reasons for this, but it is widely agreed that this is mainly due to the relative resistance of cancer cells to

introduce foreign material combined with low transgene expression *in vivo*. Thus, improved vector systems and application protocols will continue to be the biggest issues to be dealt with in cancer gene therapy in the next few years."

The Relative Skill of Those in the Art

16. The relative skill of those in the art is high.

The breadth of the claims

17. With respect to the macromolecular principle and the diseases to be treated, the claims are extremely broad with virtually any protein, polynucleotide or polysaccharide falling within the scope of the invention. Claims 9, 10, 19 and 20 narrow the scope to insulin, calcitonin, growth hormone, parathyroid hormone or erythropoietin. Claims 11 and 21 narrow the scope to insulin and its derivatives.

The Amount of Direction or Guidance Presented and the Presence of Working Examples

18. Despite the breadth of the claims, the specification provides only one working example: a pharmaceutical composition comprising insulin, a bile salt and propyl gallate and a method to treat diabetes. The specification recites a laundry list of possible proteins, polynucleotides and polysaccharides that could potentially be used in the claimed compositions but it does not provide any specific examples other than insulin. In addition, the specification fails to provide detailed guidance on which specific diseases can be treated by the macromolecules and by what methods. How are the patient populations to be identified? How are the compositions to be administered and in what dose? Is the active ingredient compatible with the bile salt? How does the ratio and dose of macromolecule need to be adjusted in response to the effect of the bile salt on uptake?

The Quantity of Experimentation Necessary

19. Considering the factors above, the skilled artisan would be burdened with undue experimentation in determining how to use compositions comprising all macromolecular principles that fall within the scope of the claims. Years of inventive effort would be required to make all the compositions within the scope of the claims and determine which diseases to treat with them and by what method.

20. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 23 recites the limitation "the aromatic alcohol" in claim 26. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

22. Applicant's arguments, see pages 8-10, filed 10/27/2006, with respect to Soltero *et al.* have been fully considered and are persuasive. The rejection of claims 1, 6-10, 12, 13, 18-20 and 23-25 has been withdrawn.

Claim Rejections - 35 USC § 103

23. Applicant's arguments with respect to claims 2-5, 11, 13, 14, 21 and 22 have been considered but are moot in view of the new ground(s) of rejection.

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. Claims 1-15 and 18-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over New (U.S. Patent No. 5,853,748) in view of Makino *et al.* (JP 56138168A), Modi *et al.* (U.S. Patent No. 5,653,987) and Desai (U.S. Patent No. 5,206,219). Regarding claim 1, New teaches a pharmaceutical composition of a macromolecular principle (insulin), a bile acid (chenodeoxycholic acid) and an additive that buffers the gut to pH 7.5-9 (sodium bicarbonate, example 4). Regarding claims 26 and 24, New also teaches a method of enhancing the absorption of the insulin across the intestinal well in an animal body comprising administering the insulin/chenodeoxycholic acid/sodium bicarbonate composition. Regarding claims 2 and 22, the composition comprises less than 5% by weight of water (table in example 4). Regarding claim 3, the composition is coated with an enteric coating designed to prevent digestion in the stomach (column 7, lines 37-40). Regarding claim 4, the additive, sodium bicarbonate, is present at 8.3% by weight which is great than 1% (table in example 4). Regarding claim 5, the ratio by weight of the chenodeoxycholic acid plus the additive to the insulin is 10:1 which is greater than 5:1 (table in example 4). Regarding claims 6 and 7 and 23, the composition is in the form of a solution (column 7, lines 50-55) or a solid (example 4). Regarding claims 8-11 and 18-21, the active macromolecular principle is insulin. Regarding claims 11 and 21, the composition sensitizes the subject to insulin by increasing uptake (example 4). Regarding claim 12, the non-conjugated bile acid is chenodeoxycholic acid, the acidic form of chenodeoxycholate. Regarding claim 15, the composition is for therapeutic use in a human or animal (example 4).

26. New does not teach that the additive can be propyl gallate. Makino *et al.* teach a pharmaceutical composition comprising an active ingredient and a bile acid, such as deoxycholic, cholic or apocholic acid, and an antioxidant such butylhydroxytoluene, propyl gallate or lecithin each present at 10-100,000 and 10-10,000 times that of the active ingredient, respectively (abstract). Desai teaches that antioxidants like butylated hydroxyanisole, butylated hydroxytoluene, d-α-tocopherol, and propyl gallate are commonly used in pharmaceutical compositions of insulin and other protein active ingredients (column 5, lines 5-18).

27. It would have been obvious to one of ordinary skill in the art to substitute the propyl gallate for the sodium bicarbonate in the pharmaceutical composition taught by New and to use it treat diabetes (claim 25). The skilled artisan would have been motivated to do so given that the pKa of propyl gallate is 8.11 (CRC Handbook of Chemistry and Physics) and that New teaches that additives that buffer the gut between pH 7.5 and 9 increase the bioavailability of the insulin while limiting the toxicity of the bile acids (column 5, lines 10-18). The skilled artisan would have been further motivated by Makino *et al.* who teach that the bile acid and antioxidant combination renders the pharmaceutical stable to light and heat for a long period of time (abstract), Desai who teaches that antioxidants are commonly used, and Modi *et al.* who teach that it is usual to add at least one antioxidant to prevent degradation and oxidation of pharmaceutically active ingredients (column 3, lines 33-36). There would have been a reasonable expectation of success given that that propyl gallate is commonly used in pharmaceutical compositions and has an appropriate pKa for buffering a solution between pH 7.5 and 9, and that New demonstrated that insulin and bile acids are compatible. Thus, the invention

as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

28. Regarding claim 14, it would have been obvious to one of ordinary skill in the art to substitute butyl hydroxyl anisole for the sodium bicarbonate in the pharmaceutical composition taught by New and to use it treat diabetes (claim 25). The skilled artisan would have been motivated to do so given that the pKa of butyl hydroxyl anisole is 7.5 (Ivanovic *et al.*, *Chromatographia*, **1995**, *40*, 652-6) and that New teaches that additives that buffer the gut between pH 7.5 and 9 increase the bioavailability of the insulin while limiting the toxicity of the bile acids (column 5, lines 10-18). The skilled artisan would have been further motivated by Makino *et al.* who teach that the bile acid and antioxidant combination renders the pharmaceutical stable to light and heat for a long period of time (abstract), Desai who teaches that antioxidants are commonly used, and Modi *et al.* who teach that it is usual to add at least one antioxidant to prevent degradation and oxidation of pharmaceutically active ingredients (column 3, lines 33-36). There would have been a reasonable expectation of success given that that propyl gallate is commonly used in pharmaceutical compositions and has an appropriate pKa for buffering a solution between pH 7.5 and 9, and that New demonstrated that insulin and bile acids are compatible. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

29. Regarding claims 11 and 21, it would have been further obvious to use a known insulin sensitizing agent in the pharmaceutical composition. Sonnenberg & Kotchen (*Curr. Op. Neph. Hyperten.*, **1998**, *7*, 551-5) teach that troglitazone has been approved by the FDA for the treatment of type II diabetes. The skilled artisan would have been motivated to use it in the

composition taught by New because Sonnenberg & Kotchen teach that troglitazone produced a significant, dose-dependent reduction in glycosylated hemoglobin and fasting glucose concentrations despite decreases in insulin doses in clinical trials involing diabetic patients (page 552). There would have been a reasonable expectation of success because the U.S. Food and Drug Adminitsrtaion has approved the use of troglitazone in combination with insulin (page 552). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

30. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

31. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

32. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

33. Claims 1-15 and 18-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-58 of copending Application No. 10/553,324 in view of New (U.S. Patent No. 5,853,748). Claims 57 and 58 of copending Application No. 10/553,324 recite pharmaceutical compositions comprising a

macromolecular principal, a solubilization aid and an absorption enhancer. Bile salts are recited in the Markush group of solubilization aids in both claims, and butyl hydroxy anisole and propyl gallate are recited as the absorption enhances in claims 57 and 58, respectively. It would have been obvious to select bile salts as the solubilization aids in view of New (U.S. Patent No. 5,853,748) who teaches that bile acids such as chenodeoxycholic acid increase the bioavailability of insulin (example 4), thus satisfying claims 1 & 12. The additional limitations of claims 2-11, 13-15, and 18-26 are recited in claims 32-38, 42-44, 40, 39, 45, 32, 52-55, 52, 46, 45, and 46, respectively, of copending Application No. 10/553,324. This is a provisional obviousness-type double patenting rejection.

Conclusion

34. No claims are allowed.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.

36. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

37. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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